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REMARKS

The Office Action dated January 2, 2004 presents the examination of claims 1-3, 6-7, and 10-20. Claims 1, 6, 7, and 13 are amended. Claims 2, 10, and 20 are canceled. Upon entry of this Reply, claims 1, 6-7, and 11-19 will be pending. No new matter is inserted into the application.

Related U.S. Patents

Pursuant to the discussion during the interview held on May 20, 2004, the Examiner is provided with copies of two (2) related U.S. Patents (Sümegi '337 and Sümegi '955).

Interview

Applicant's representative extends gratitude to the Examiner for the beneficial interview held at the United States Patent and Trademark Office on May 20, 2004.

Markush Group

The Examiner rejects claims 1, 3, 6, 11-18, and 20 under "judicially created doctrine" for reciting an allegedly improper Markush group. Claim 20 is canceled, thus rendering rejection thereof moot. Applicants respectfully traverse the rejection

applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Claims 1 and 6, as amended, recite an effective amount of O-(3-piperidino-2-hydroxy-1-propyl)nicotinic acid amidoxime or a pharmaceutically acceptable acid addition salt thereof. As discussed during the interview, this rejection is overcome. Therefore, withdrawal thereof is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 1-3, 6, 7, and 10-20 under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter not enabled by the specification. Claims 2, 10, and 20 are canceled, thus rendering rejection thereof moot. Applicants respectfully traverse the rejection applied to the pending claims. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Claims 1 and 6, as amended, recite a pharmaceutical composition having antitumor activity with reduced side effect(s) comprising an effective amount of a known active substance having antitumor effect selected from the group consisting of pyrimidine derivatives or, optionally, a pharmaceutically acceptable acid addition salt thereof, and an effective amount of O-(3-piperidino-2-hydroxy-1-

propyl)nicotinic acid amidoxime or a pharmaceutically acceptable acid addition salt thereof.

Applicants respectfully submit that the combination of combination of O-(3-piperidino-2-hydroxy-1-propyl)nicotinic acid amidoxime (or a pharmaceutically acceptable acid addition salt thereof) and pyrimidine derivatives (or a pharmaceutically acceptable acid addition salt thereof) are enabled by the specification.

First, as discussed during the interview, pyrimidine derivatives are well known in the art to have antitumor activity. As evidence thereof, Applicants again refer the Examiner to pages 1404 to 1408 of *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th Ed. (McGraw-Hill, NY) (attached hereto as Exhibit 1). On page 1405, in addition to fluorouracil, fluoropyrimidine, and cytidine analogs such as floxuridine, cytarabine, and gemcitabine are described. On this page below the chemical formulae in column 1, last three lines and column 2, first two lines, it is stated that gemcitabine "has promising activity in various human solid tumors, including pancreatic, lung and ovarian cancer". From page 1407, column 2, section "Therapeutic Uses" it can be seen that 5-fluorouracil (which is another name of fluorouracil) can be used in metastatic carcinomas of the breast

and the gastrointestinal tract, as well as in the carcinoma of the ovary, cervix, urinary bladder, prostate, pancreas and oropharyngeal areas. Floxuridine is used for treatment of metastatic carcinoma of the colon or following resection of hepatic metastases (page 1407, column 2, last three lines and page 1408, column 1, first line). Cytarabine is used in therapy of acute myelocytic leukemia (page 1408, column 2, section "Cytarabine").

Thus, in the literature it can be found which sort of tumor can be treated with a known antitumor agent. The several toxicities that accompany the use of an antitumor agent can be equally found in the literature (see the cited manual, page 1408, column 1, last section "Clinical Toxicities").

Consequently, it is not necessary to carry out experiments to determine the antitumor agent to be used by an oncologist. The present invention is directed to administration of an antitumor agent that the oncologist has chosen and O-(3-piperidino-2-hydroxy-1-propyl)nicotinic acid amidoxime or a pharmaceutically acceptable acid addition salt thereof to a patient to reduce the toxic side effects of the antitumor agent.

In addition, the attached Declaration under 37 C.F.R. § 1.132 executed by the present inventor, Dr. Balázs SÜMEGI, provides additional experimental data showing the unexpected effects of

compound L and fluorouracil on tumor growth (attached hereto as Exhibit 2). Specifically, as summarized in the table on page 4 of the Declaration, combined therapy with increasing doses of fluorouracil and compound L effectively reduced the gastrointestinal toxicity of fluorouracil alone, even when fluorouracil was administered in a dose of as high as 150 mg/kg.

These results unequivocally show that the instant claims are enabled under 35 U.S.C. § 112, first paragraph. For these reasons, withdrawal of the instant rejection is respectfully requested.

Disclosure

The Examiner objects to the disclosure for the recitation of "known active substance" in claims 1 and 6. Applicants respectfully traverse. Reconsideration and withdrawal of the instant objection are respectfully requested.

The Examiner asserts that "known active substance" is relative in definition. Applicants respectfully disagree. In this regard, the same terminology was used and approved of by the United States Patent and Trademark Office as shown in U.S. Patents 6,720,337, and 6,656,995, as well as in the parent application (application no. 09/446,064, now U.S. Patent 6,440,998) of the present application. Therefore, "known active substance" is not relative in definition as

applied to the instant technology, and withdrawal of the instant rejection is respectfully requested.

Conclusion

As the above remarks and/or claim amendments fully address, overcome, render moot, or otherwise accommodate the outstanding rejections in the Office Action, the present application is in condition for allowance. The Examiner is respectfully requested to issue a Notice of Allowance indicating that claims 1, 3, 6-7, and 11-19 are allowed.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

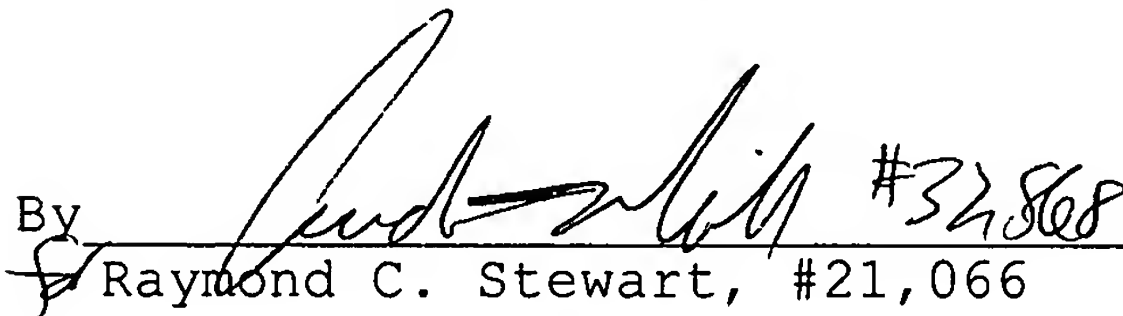
Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of three (3) months to July 2, 2004, in which to file a reply to the Office Action. The required fee of \$950.00 is enclosed herewith.


Application Number 10/084,095

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By  #32868
Raymond C. Stewart, #21,066


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Attachments: Exhibit 1: Goodman & Gilman's The Pharmacological
Basis of Therapeutics
Exhibit 2: Declaration Under 37 C.F.R. 1.132 of
Balázs SÜMEGI and Curriculum Vitae
Letter to PTO submitting U.S. 6,720,337 B2 and
U.S. 6,656,955 B2

GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Tenth Edition

McGraw-Hill
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tumor regression in osteosarcoma and in combination therapy of leukemias and non-Hodgkin's lymphomas. A 6- to 72-hour infusion of relatively large amounts of methotrexate may be employed intermittently (from 250 mg to 7.5 g/m² or more), but only when leucovorin rescue is used. Such regimens produce cytotoxic concentrations of drug in the cerebrospinal fluid (CSF) and protect against leukemic meningitis. A typical regimen includes the infusion of methotrexate for 6 hours followed by leucovorin at a dose of 15 mg/m² every 6 hours for seven doses, with the goal of rescuing normal cells and thereby preventing toxicity. Other dosage regimens also are used. The administration of methotrexate in high dosage has the potential for serious toxicity and should be performed only by experienced chemotherapists who are able to monitor concentrations of methotrexate in plasma. If methotrexate values measured 48 hours after drug administration are 1 μ M or higher, higher doses (100 mg/m²) of leucovorin must be given until the plasma concentration of methotrexate falls below the toxic threshold of 2×10^{-8} M (Stoller *et al.*, 1977). With appropriate precautions, these schedules are relatively free of toxicity. It is imperative to maintain the output of a large volume of alkaline urine, since methotrexate precipitates in the renal tubules in acidic urine. In the presence of malignant effusions, delayed clearance may cause severe toxicity. In patients who become oliguric, isolated reports suggest that continuous-flow hemodialysis can eliminate methotrexate at a rate approximating 50% of the clearance rate in patients with intact renal function (Wall *et al.*, 1996). Methotrexate in high doses with leucovorin rescue has been studied clinically for many years with promising results in osteosarcoma, childhood leukemia, and non-Hodgkin's lymphoma, although the optimal timing and dose of leucovorin required and the optimal schedule of methotrexate administration remain to be established (Ackland and Schilsky, 1987).

Clinical Toxicities. As previously stated, the primary toxicities of methotrexate affect the bone marrow and the intestinal epithelium. Such patients may be at risk for spontaneous hemorrhage or life-threatening infection, and they may require prophylactic transfusion of platelets and broad-spectrum antibiotics if febrile. Side effects usually disappear within 2 weeks, but prolonged suppression of the bone marrow may occur in patients with compromised renal function who have delayed excretion of the drug. The dosage of methotrexate must be reduced in proportion to any reduction in creatinine clearance.

Additional toxicities of methotrexate include alopecia, dermatitis, interstitial pneumonitis, nephrotoxicity, defective oogenesis or spermatogenesis, abortion, and teratogenesis. Hepatic dysfunction is usually reversible but sometimes leads to cirrhosis after long-term continuous treatment, as in patients

with psoriasis. Intrathecal administration of methotrexate often causes meningismus and an inflammatory response in the CSF. Seizures, coma, and death may occur rarely. Leucovorin does not reverse neurotoxicity.

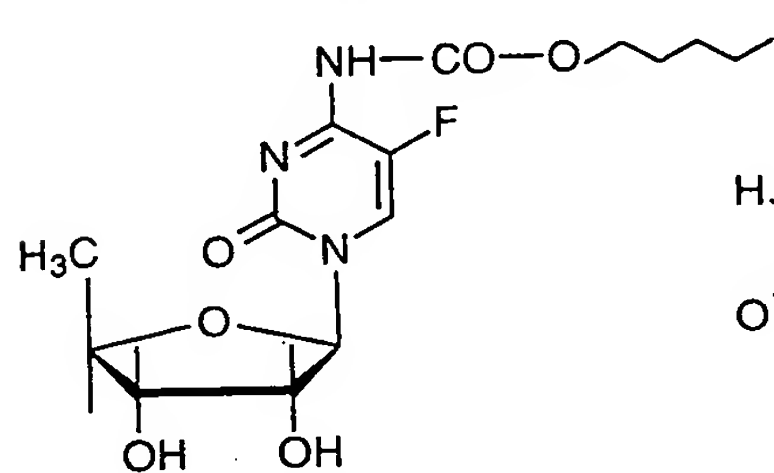
PYRIMIDINE ANALOGS

This class of agents encompasses a diverse and interesting group of drugs that have in common the capacity to inhibit the biosynthesis of pyrimidine nucleotides or to mimic these natural metabolites to such an extent that the analogs interfere with the synthesis or function of nucleic acids. Analogs of deoxycytidine and thymidine have been synthesized as inhibitors of DNA synthesis, and an analog of uracil, 5-fluorouracil, effectively inhibits both RNA function and/or processing and synthesis of thymidylate (*see* Figure 52-8). Drugs in this group have been employed in the treatment of diverse afflictions, including neoplastic diseases, psoriasis, and infections caused by fungi and DNA-containing viruses. The pathways for metabolic activation and degradation of these compounds during systemic administration present opportunities for the development of synergistic combination therapies with other clinically effective drugs.

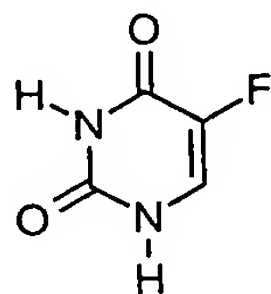
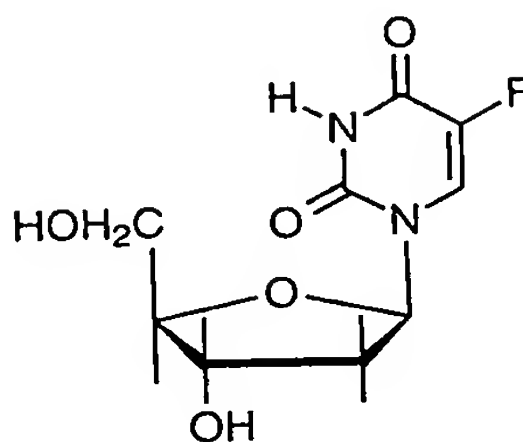
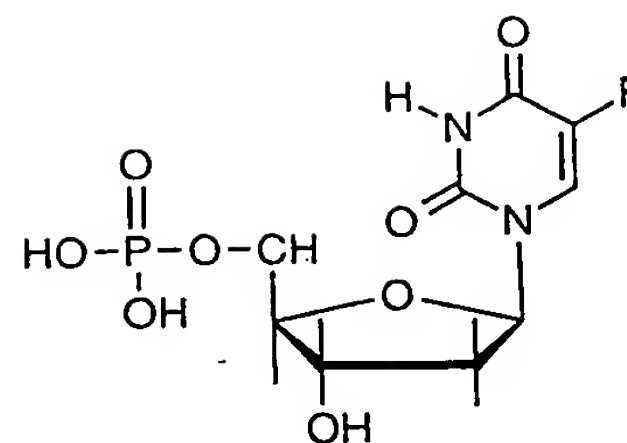
General Mechanism of Action. The best-characterized agents in this class are the halogenated pyrimidines, a group that includes *fluorouracil* (5-fluorouracil, or 5-FU), *floxuridine* (5-fluoro-2'-deoxyuridine, or 5-FUdR), and *idoxuridine* (5-iododeoxyuridine; *see* Chapter 50). If one compares the van der Waals radii of the various 5-position substituents, the dimension of the fluorine atom resembles that of hydrogen, whereas the bromine and iodine atoms are larger and close in size to the methyl group. Thus, idoxuridine behaves as an analog of thymidine, and its primary biological action results from its phosphorylation and ultimate incorporation into DNA in place of thymidylate. In 5-FU, the smaller fluorine at position 5 allows the molecule to mimic uracil biochemically. However, the fluorine-carbon bond is much tighter than that of C—H and prevents the methylation of the 5 position of 5-FU by thymidylate synthase. Instead, in the presence of the physiological cofactor 5,10-methylene tetrahydrofolate, the fluoropyrimidine locks the enzyme in an inhibited state. Thus, substitution of a halogen atom of the correct dimensions can produce a molecule that sufficiently resembles a natural pyrimidine to interact with enzymes of pyrimidine metabolism but at the same time interferes drastically with certain other aspects of pyrimidine action.

A number of 5-FU analogs have reached the clinic. The most important of these is *capecitabine* (N4-pentoxycarbonyl-5'-deoxy-5-fluorocytidine), a drug with proven activity against colon and breast cancers. This orally administered agent is converted to 5'-deoxy-5-fluorocytidine by carboxylesterase activity in liver and other normal and malignant tissues. From that point, it is converted to 5'-deoxy-fluorodeoxyuridine by cytidine deaminase. The final step in its activation occurs when thymidine

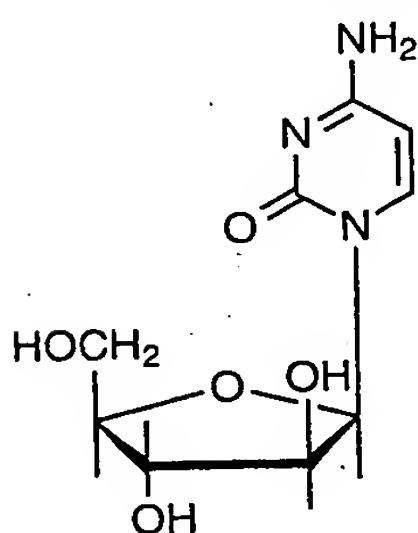
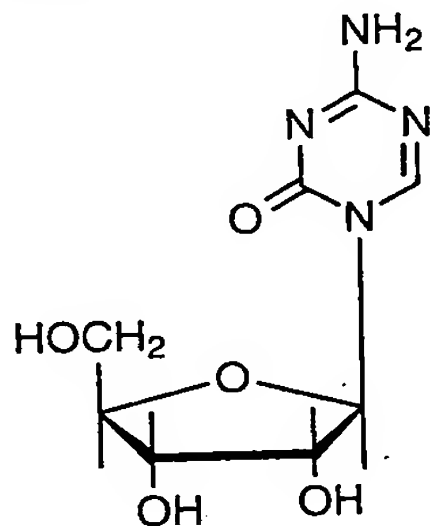
FLUOROPYRIMIDINE ANALOGS



Capecitabine

5-Fluorouracil
(5-FU)5-Fluorodeoxyuridine
(floxuridine)5-Fluorodeoxyuridine
monophosphate
(active metabolite)

CYTIDINE ANALOGS

Cytosine arabinoside
(cytarabine; AraC)

5-Azacytidine

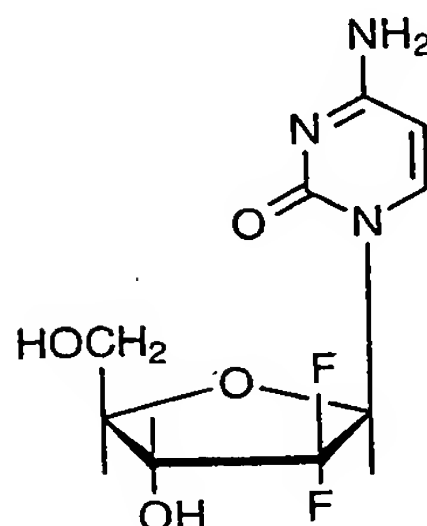
2', 2'-Difluorodeoxycytidine
(gemcitabine)

Figure 52-8. Structures of available pyrimidine analogs.

phosphorylase cleaves off the 5'-deoxy sugar, leaving intracellular 5-FU. Tumors with elevated thymidine phosphorylase activity seem particularly susceptible to this drug (Ishikawa *et al.*, 1998).

Nucleotides in RNA and DNA contain ribose and 2'-deoxyribose, respectively. Among the various modifications of the sugar moiety that have been attempted, the replacement of the ribose of cytidine with arabinose has yielded a useful chemotherapeutic agent, *cytarabine* (AraC). As may be seen in Figure 52-8, the hydroxyl group in this molecule is attached to the 2'-carbon in the β , or upward, configuration, as compared with the α , or downward, position of the 2'-hydroxyl in ribose. The arabinose analog is recognized enzymatically as a 2'-deoxyriboside; it is phosphorylated to a nucleoside triphosphate that competes with dCTP for incorporation into DNA (Chabner *et al.*, 2001), where it blocks elongation of the DNA strand and its template function.

Two other cytidine analogs have received extensive clinical evaluation. 5-Azacytidine, an inhibitor of DNA methylation as well as a cytidine antimetabolite, becomes incorporated predominantly into RNA and has antileukemic as well as differentiating actions *in vitro*. A newer analog, 2',2'-difluorodeoxycytidine (*gemcitabine*), becomes incorporated into DNA and inhibits the elongation of nascent DNA strands (see Figure 52-8). It has

promising activity in various human solid tumors, including pancreatic, lung, and ovarian cancer.

Fluorouracil and Floxuridine
(Fluorodeoxyuridine)

Mechanism of Action. 5-FU requires enzymatic conversion to the nucleotide (ribosylation and phosphorylation) in order to exert its cytotoxic activity (Figure 52-9). Several routes are available for the formation of the 5'-monophosphate nucleotide (F-UMP) in animal cells. 5-FU may be converted to fluorouridine by uridine phosphorylase and then to F-UMP by uridine kinase, or it may react directly with 5-phosphoribosyl-1-pyrophosphate (PRPP), in a reaction catalyzed by the enzyme orotate phosphoribosyl transferase, to form F-UMP. Many metabolic pathways are available to F-UMP, including incorporation into RNA. A reaction sequence crucial for antineoplastic activity involves reduction of the diphosphate nucleotide by the enzyme ribonucleotide diphosphate reductase to the deoxynucleotide level and the eventual formation of 5-fluoro-2'-deoxyuridine-5'-phosphate (F-dUMP). 5-FU also may be converted directly to the deoxyriboside 5-FUdR by the enzyme thymidine phosphorylase and further to F-dUMP, a potent

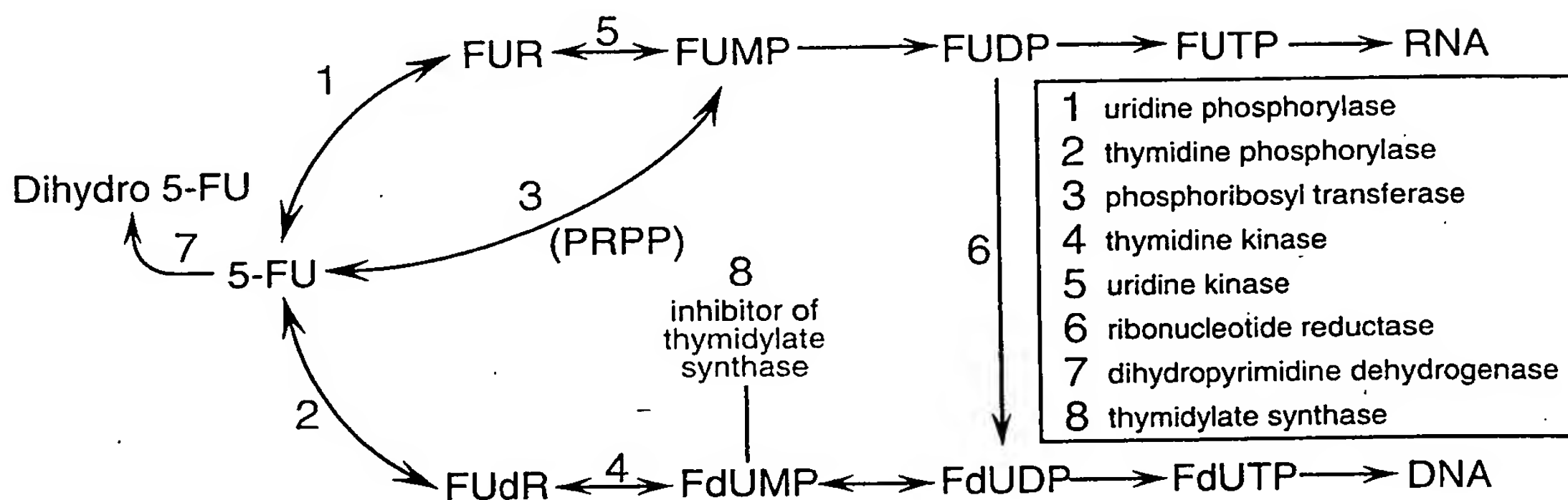


Figure 52-9. Activation pathways for 5-fluorouracil (5-FU) and 5-floxuridine (FUR).

FUDP, floxuridine diphosphate; FUMP, floxuridine monophosphate; FUTP, floxuridine triphosphate; FdR, fluorodeoxyuridine; FdUDP, fluorodeoxyuridine diphosphate; FdUMP, fluorodeoxyuridine monophosphate; FdUTP, fluorodeoxyuridine triphosphate; PRPP, 5-phosphoribosyl-1-pyrophosphate.

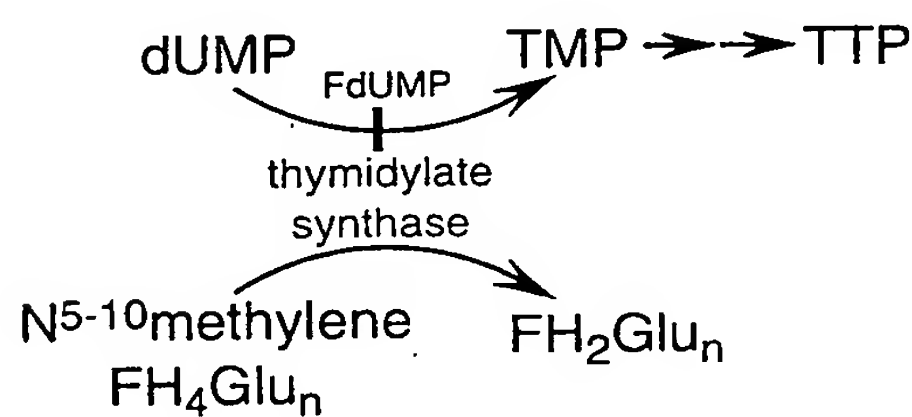
inhibitor of thymidylate synthesis, by thymidine kinase. This complex metabolic pathway for the generation of F-dUMP may be bypassed through use of the deoxyribonucleoside of fluorouracil—floxuridine (fluorodeoxyuridine, FdR)—which is converted directly to F-dUMP by thymidine kinase.

The interaction between F-dUMP and the enzyme thymidylate synthase leads to deletion of TTP, a necessary constituent of DNA (Figure 52-10). The folate cofactor, 5,10-methylenetetrahydrofolate, and F-dUMP form a covalently bound ternary complex with the enzyme. This inhibitory complex resembles the transition state formed during the normal enzymatic reaction when dUMP is converted to thymidylate. Although the physio-

logical complex progresses to the synthesis of thymidylate by transfer of the methylene group and two hydrogen atoms from folate to dUMP, this reaction is blocked in the inhibitory complex by the stability of the fluorine carbon bond on F-dUMP; sustained inhibition of the enzyme results (Santi *et al.*, 1974).

5-FU also is incorporated into both RNA and DNA. In 5-FU-treated cells, both F-dUTP and dUTP (the substrate that accumulates behind the blocked thymidylate synthase reaction) incorporate into DNA in place of the depleted physiological TTP. The significance of the incorporation of F-dUTP and dUTP into DNA is unclear (Canman *et al.*, 1993). Presumably, the incorporation of deoxyuridylate and/or fluorodeoxyuridylate into DNA would call into action the excision-repair process. This process may result in DNA strand breakage because DNA repair requires TTP, but this substrate is lacking as a result of thymidylate synthase inhibition (Mauro *et al.*, 1993). 5-FU incorporation into RNA also causes toxicity as the result of major effects on both the processing and functions of RNA (Armstrong, 1989; Danenberg *et al.*, 1990).

A number of biochemical mechanisms have been identified that are associated with resistance to the cytotoxic effects of 5-FU or floxuridine. These mechanisms include loss or decreased activity of the enzymes necessary for activation of 5-FU, decreased pyrimidine monophosphate kinase (which decreases incorporation into RNA), amplification of thymidylate synthase (Washtien, 1982), and altered thymidylate synthase that is not inhibited by F-dUMP (Barbour *et al.*, 1990). Both experimental studies and clinical trials support the position that the response to 5-FU correlates significantly with low levels of the degradative enzymes, dihydrouracil dehydrogenase and thymidine phosphorylase, and a low level of expression of the target enzyme, thymidylate synthase (van Triest *et al.*, 2000). Recent investigations have demonstrated that the level of thymidylate synthase is finely controlled by an autoregulatory feedback mechanism wherein the thymidylate synthase protein interacts with and controls the translational efficiency of its own messenger RNA. This mechanism provides for the rapid modulation of the level of thymidylate synthase necessary for cellular division and also



Other Actions of 5-FU nucleotides:

- Inhibition of RNA processing
- Incorporation into DNA

Figure 52-10. Site of action of 5-fluoro-2'-deoxyuridine-5'-phosphate (5-FdUMP).

5-FU, 5-fluorouracil; dUMP, deoxyuridine monophosphate; TMP, thymidine monophosphate; TTP, thymidine triphosphate; FdUMP, fluorodeoxyuridine monophosphate; FH₂Glu_n, dihydrofolate polyglutamate; FH₄Glu_n, tetrahydrofolate polyglutamate

Table 52-2
Modulators of Cytotoxic Activity
of 5-Fluorouracil (5-FU)

MODULATOR	PURPORTED MECHANISM(S) OF INTERACTION
Cisplatin	Enhanced DNA strand breaks secondary to decreased repair Enhanced thymidylate synthase inhibition
Interferon	Enhanced 5-FU anabolism Decreased "rebound" synthesis of thymidylate synthase
Leucovorin	Enhanced thymidylate synthase inhibition
Methotrexate	Enhanced 5-FU anabolism Enhanced RNA incorporation
PALA*	Enhanced 5-FU anabolism Enhanced RNA incorporation
Uridine	Diminished RNA incorporation (? selective rescue for normal cells)

*PALA, *N*-phosphonoacetyl-L-aspartate.

may be an important mechanism by which malignant cells become rapidly insensitive to the effects of 5-fluorouracil (Chu *et al.*, 1991; Swain *et al.*, 1989). Some malignant cells appear to have insufficient concentrations of 5,10-methylene tetrahydrofolate and, thus, cannot form maximal levels of the inhibited ternary complex with thymidylate synthase. Addition of exogenous folate in the form of 5-formyl-tetrahydrofolate (leucovorin) increases formation of the complex in both laboratory and clinical experiments and has enhanced responses to 5-FU in clinical trials (Ullman *et al.*, 1978; Grogan *et al.*, 1993). Except for inadequate intracellular folate pools, it is not established which (if any) of the other mechanisms is associated with clinical resistance to 5-FU and its derivatives (Grem *et al.*, 1987).

In addition to leucovorin, a number of other agents have been combined with 5-FU in attempts to enhance the cytotoxic activity through biochemical modulation. These agents, along with their proposed mechanisms of interaction, are shown in Table 52-2. The most clinically interesting combinations with 5-FU include methotrexate, interferon, leucovorin, or cisplatin, all of which are currently under investigation to define their ultimate clinical roles. Agents that inhibit early steps in pyrimidine biosynthesis, such as PALA (*N*-phosphonoacetyl-L-aspartate), an inhibitor of aspartate transcarbamylase, provide synergistic interaction with 5-FU in experimental systems, but these combinations have no proven clinical value (Grem *et al.*, 1988). Methotrexate, by inhibiting purine synthesis and increasing cellular pools of PRPP, enhances the activation of 5-FU and increases antitumor activity of 5-FU when given prior to but not following 5-FU. In clinical trials, the combination of cisplatin and 5-FU has yielded impressive responses in tumors of the upper aerodigestive tract, but the molecular basis of their interaction is not well understood (Grem, 2001).

Absorption, Fate, and Excretion. 5-FU and floxuridine are administered parenterally, since absorption after ingestion of

the drugs is unpredictable and incomplete. Metabolic degradation occurs in many tissues, particularly the liver. Floxuridine is converted by thymidine or deoxyuridine phosphorylases into 5-FU. 5-FU is inactivated by reduction of the pyrimidine ring; this reaction is carried out by dihydropyrimidine dehydrogenase (DPD), which is found in liver, intestinal mucosa, tumor cells, and other tissues. Inherited deficiency of this enzyme leads to greatly increased sensitivity to the drug (Lu *et al.*, 1993; Milano *et al.*, 1999). The rare individual who totally lacks this enzyme may experience profound drug toxicity following conventional doses of the drug. DPD deficiency can be detected either by enzymatic or molecular assays using peripheral white blood cells, or by determining the plasma ratio of 5-FU to its metabolite, 5-fluoro-5,6-dihydrouracil, which is ultimately degraded to α -fluoro- β -alanine (Heidelberger, 1975; Zhang *et al.*, 1992).

Rapid intravenous administration of 5-FU produces plasma concentrations of 0.1 to 1.0 mM; plasma clearance is rapid ($t_{1/2}$ 10 to 20 minutes). Urinary excretion of a single dose of 5-FU given intravenously amounts to only 5% to 10% in 24 hours. Although the liver contains high concentrations of DPD, dosage does not have to be modified in patients with hepatic dysfunction, presumably because of degradation of the drug at extrahepatic sites or by vast excess of this enzyme in the liver. Given by continuous intravenous infusion for 24 to 120 hours, 5-FU achieves plasma concentrations in the range of 0.5 to 8.0 μ M. 5-FU readily enters the CSF, and concentrations greater than 0.01 μ M are sustained for up to 12 hours following conventional doses (Grem, 2001).

Capecitabine is well absorbed orally, yielding high plasma concentrations of 5'-deoxy-fluorodeoxyuridine (5'-dFdU), which disappears with a half-life of about 1 hour. 5-FU levels are less than 10% of those of 5'-dFdU. Liver dysfunction delays the conversion of the parent compound to 5'-dFdU and 5-FU, but there is no consistent effect on toxicity (Twelves *et al.*, 1999).

Therapeutic Uses. 5-Fluorouracil. Accumulated experience with 5-FU (ADRUCIL) indicates that the drug produces partial responses in 10% to 20% of patients with metastatic carcinomas of the breast and the gastrointestinal tract; beneficial effects also have been reported in carcinoma of the ovary, cervix, urinary bladder, prostate, pancreas, and oropharyngeal areas. For average-risk patients in good nutritional status with adequate hematopoietic function, the weekly dosage regimen employs 750 mg/m² alone or 500 to 600 mg/m² with leucovorin once each week for 6 of 8 weeks. Other regimens use daily doses of 500 mg/m² for 5 days, repeated in monthly cycles. When used with leucovorin, daily doses of 5-FU must be reduced to 375 to 425 mg/m² for 5 days because of mucositis and diarrhea. It also has been given as a continuous infusion for up to 21 days (300 mg/m² per day), or as a biweekly 48-hour continuous infusion (de Gramont *et al.*, 1998).

Floxuridine (FUdR). FUdR (fluorodeoxyuridine; FUDR) is used primarily by continuous infusion into the hepatic artery for treatment of metastatic carcinoma of the colon

or following resection of hepatic metastases (Kemeny *et al.*, 1999); the response rate to such infusion is 40% to 50%, or double that observed with intravenous administration. Intrahepatic arterial infusion for 14 to 21 days may be used with minimal systemic toxicity. However, there is a significant risk of biliary sclerosis if this route is used for multiple cycles of therapy (Kemeny *et al.*, 1987; Hohn *et al.*, 1986). Continuous infusion of floxuridine into the arterial blood supply of tumors at other sites, such as in the head and neck region, may provide beneficial clinical effects. With any of these regimens, treatment should be discontinued at the earliest manifestation of toxicity (usually stomatitis or diarrhea) because the maximal effects of bone marrow suppression and gut toxicity will not be evident until days 7 to 14.

Capecitabine (XELODA). Capecitabine is approved by the United States Food and Drug Administration (FDA) for the treatment of metastatic breast cancer in patients who have not responded to a regimen of paclitaxel and an anthracycline antibiotic (*see below*). The recommended dose is 2500 mg/m² daily, given orally in two divided doses with food, for 2 weeks followed by a rest period of 1 week. This cycle is then repeated two more times.

Combination Therapy. Higher response rates are seen when 5-FU is used in combination with other agents, such as cyclophosphamide and methotrexate (breast cancer), cisplatin (head and neck cancer), and with leucovorin in colon cancer (*see Table 52-2*). The use of 5-FU in combination regimens has improved survival in the adjuvant treatment for breast cancer (Early Breast Cancer Trialists Collaborative Group, 1988) and, with leucovorin, for colorectal cancer (Wolmark *et al.*, 1993). 5-FU is a potent radiation sensitizer and is being used with concurrent radiotherapy for primary therapy of locally advanced tumors of the head and neck, esophagus, lung, and rectum. 5-FU is used widely with very favorable results for the topical treatment of premalignant keratoses of the skin and multiple superficial basal cell carcinomas. It also is effective in severe recalcitrant psoriasis (Alper *et al.*, 1985).

Clinical Toxicities. The clinical manifestations of toxicity caused by 5-FU and floxuridine are similar and may be difficult to anticipate because of their delayed appearance. The earliest untoward symptoms during a course of therapy are anorexia and nausea; these are followed by stomatitis and diarrhea, which constitute reliable warning signs that a sufficient dose has been administered. Mucosal ulcerations occur throughout the gastrointestinal tract and may lead to fulminant diarrhea, shock, and death, particularly in patients who are receiving continuous infusions of 5-FU or in those receiving 5-FU with leucovorin. The major toxic effects of bolus-dose regimens result from the myelosuppressive action of these drugs. The nadir of leukopenia

is usually between days 9 and 14 after the first injection of drug. Thrombocytopenia and anemia also may occur. Loss of hair, occasionally progressing to total alopecia, nail changes, dermatitis, and increased pigmentation and atrophy of the skin may be encountered. Neurological manifestations, including an acute cerebellar syndrome, have been reported, and myelopathy has been observed after the intrathecal administration of 5-FU. Cardiac toxicity, particularly acute chest pain with evidence of ischemia in the electrocardiogram, also may occur. The low therapeutic indices of these agents emphasize the need for very skillful supervision by physicians familiar with the action of the fluorinated pyrimidines and the possible hazards of chemotherapy.

Capecitabine causes much the same spectrum of toxicities as 5-FU (diarrhea, myelosuppression), but also a progressive hand-foot syndrome consisting of erythema, desquamation, pain, and sensitivity to touch of the palms and soles.

Cytarabine (Cytosine Arabinoside; AraC)

Cytarabine (1- β -D-arabinofuranosylcytosine; AraC) is the most important antimetabolite used in the therapy of acute myelocytic leukemia. It is the single most effective agent for induction of remission in this disease (for review, *see Garcia-Carbonero et al.*, 2001).

Mechanism of Action. This compound is an analog of 2'-deoxycytidine with the 2'-hydroxyl in a position *trans* to the 3'-hydroxyl of the sugar, as shown in Figure 52-8. The 2'-hydroxyl causes steric hindrance to the rotation of the pyrimidine base around the nucleosidic bond. The bases of polyarabinonucleotides cannot stack normally, as do the bases of polydeoxynucleotides.

AraC penetrates cells by a carrier-mediated process shared by physiological nucleosides. As with most purine and pyrimidine antimetabolites, cytarabine must be "activated" by conversion to the 5'-monophosphate nucleotide (AraCMP), a reaction catalyzed by deoxycytidine kinase. AraCMP can then react with appropriate nucleotide kinases to form the diphosphate and triphosphate nucleotides (AraCDP and AraCTP). AraC competes with the physiological substrate deoxycytidine 5'-triphosphate (dCTP) for incorporation into DNA by DNA polymerases. The incorporated AraCMP residue is a potent inhibitor of DNA polymerase. The effects of AraC on DNA polymerase activity extend not only to DNA chain elongation during semiconservative DNA replication, but also to DNA repair. There is a significant relationship between inhibition of DNA synthesis and the total amount of AraC incorporated into DNA. Thus, incorporation of about five molecules of AraC per 10⁴ bases of DNA decreases cellular clonogenicity by about 50%.

AraC also causes an unusual reiteration of DNA segments, thus increasing the possibility of recombination, crossover, and gene amplification. In addition, AraC is converted intracellularly to AraCDP-choline, an analog of the physiological CDP-choline, which inhibits the synthesis of membrane glycoproteins and glycolipids. Furthermore, AraCMP inhibits the transfer of galactose, *N*-acetylglucosamine, and sialic acid to cell-surface glycoproteins, and AraCTP inhibits the synthesis of CMP-